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Multimodal Magnetic Resonance Imaging Assessments of Kidney Disease Severity in Autosomal Recessive Polycystic Kidney Disease

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INTRODUCTION

Autosomal recessive polycystic kidney disease (ARPKD) is a rare, potentially fatal genetic disorder affecting approximately 1 in 20,000 children. ARPKD is characterized by diffuse renal microcysts that become more prominent over time resulting in early kidney failure in 50% of children with ARPKD.[1] Unfortunately, there are currently no treatments to prevent ARPKD kidney disease progression. One of the key challenges to developing and evaluating potential therapies for ARPKD is the lack of effective biomarkers to identify patients at high risk of progression and to assess kidney disease progression during a clinical trial.[1,2] Except for the most severely affected infants, the rates of glomerular filtration rate decline are highly variable in patients with ARPKD.[1,3,4] Further, total kidney volume, which has been extensively validated as a clinical biomarker for autosomal dominant polycystic kidney disease, is unfortunately not a useful biomarker for ARPKD kidney disease, because the kidneys of patients with ARPKD stabilize in size despite progressive disease.[5] Further, published studies demonstrate that there is no relationship between total kidney volume and the rate of estimated glomerular filtration rate (eGFR) decline in ARPKD.[4] As such, improved biomarkers are still needed to sensitively and reliably detect and stratify ARPKD kidney disease.

Building on our previous work in rodent models of ARPKD,[6,7] the overall goal of this first-in-patients-with-ARPKD pilot study was to determine the capability of 3 novel quantitative MRI kidney imaging biomarkers: T_1 and T_2 relaxation time maps of kidney cystic burden from magnetic resonance fingerprinting (MRF)[8] and kidney cortical perfusion from arterial spin labeling (ASL)[9] to assess kidney disease in patients with ARPKD across the spectrum of disease severity in comparison to healthy young adult volunteers.

RESULTS

In this initial study, patients with ARPKD (n = 13, 5 males and 8 females, aged 6–22 years) were evaluated both as a single cohort as well as 2 subgroups based on kidney function: (i) early chronic kidney disease (CKD) (n = 7; median eGFR = 98 ml/min per 1.73 m^2, range = 91–109 ml/min per 1.73 m^2), and (ii) mild to moderate CKD (n = 6; median eGFR = 74 ml/min per 1.73 m^2, range = 52–87 ml/min per 1.73 m^2) (Table 1). Patients with ARPKD in the mild to moderate CKD group were slightly older as expected given the progressive nature of the disease (median age = 12 vs. 7 years). The

Table 1. ARPKD subject demographics and clinical data

Metric	All ARPKD subjects	ARPKD subjects with early CKD	ARPKD subjects with mild to moderate CKD
Subjects (gender distribution)	13 (5M/8F)	7 (2M/5F)	6 (3M/3F)
Age: median (range)	10 (6–22) yr	7 (6–22) yr	12 (6–21) yr
eGFR: median (range)	91 (52–109) ml/min per 1.73 m^2	98 (91–109) ml/min per 1.73 m^2	74 (52–87) ml/min per 1.73 m^2
Subjects with systemic hypertension	11	5	6
Subjects prescribed ACE/ARB	9	4	5
Urine protein-to-creatinine ratio: median (range)	0.1 (0.09–0.2) mg/mg	0.13 (0.1–0.2) mg/mg	0.1 (0.09–0.2) mg/mg

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARPKD, autosomal recessive polycystic disease; eGFR, estimated glomerular filtration rate; F, female; M, male.

majority of patients with ARPKD had hypertension (11/13) and were receiving angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy as typical (9/13). Proteinuria was minimal for all ARPKD subjects (range = 0.09–0.2 mg/mg). Healthy young adult volunteers reported no known history of kidney disease ($n = 8$, aged 18–36 years). Additional information on the study methods is included in the Supplementary Materials.

In Figure 1, we show representative kidney T_1 (a–c) and T_2 (d–f) maps (obtained from novel MRF[8]), and kidney perfusion maps (g–i) (obtained from kidney ASL[9]) for a healthy volunteer (left column) and 2 patients with ARPKD (middle and right columns). The patients with ARPKD kidneys show visible increases in T_1 and T_2, consistent with increased kidney cystic burden as well as decreases in kidney perfusion in comparison to each other as well as the healthy volunteer. Importantly, the ARPKD subject with mild to moderate CKD (right column) shows visibly increased kidney T_1 and T_2 values and decreased perfusion as compared to the ARPKD subject with early CKD (middle column) despite relatively similar eGFR (87 vs. 101 ml/min per 1.73 m^2, respectively). These initial observations suggest that differences in T_1, T_2 and/or perfusion may be able to sensitively identify and measure early disease and differentiate early from more severe disease, even in patients with relatively intact kidney function.

A statistical comparison of the kidney MRI assessments showed significant increases in both kidney T_1 and T_2 as well as significantly reduced perfusion for the entire cohort of patients with ARPKD in comparison to the healthy volunteers (mean T_1: 2218 vs. 1473 ms; mean T2: 97 vs. 69 ms; mean cortical perfusion: 72 vs. 139 ml/min/100 g; $P \leq 0.001$ for all 3 measures) (see Supplementary Statistical Analysis section). Even with these limited cohort sizes, these multimodal MRI assessments consistently detected significant differences in mean kidney T_1 and T_2 as follows: (i) between the cohorts of patients with ARPKD with early and mild to moderate CKD ($P = 0.02$ and $P = 0.005$, respectively), and (ii) between the patients with ARPKD with early CKD and the healthy volunteers ($P < 0.001$). The ASL-based perfusion assessment showed a significant difference between the patients with ARPKD with early CKD and healthy volunteers ($P = 0.02$). However, ASL differences detected between the early versus mild to moderate CKD ARPKD cohorts was not significant ($P = 0.20$) (Figure 1 j–l). Statistical associations between the MRI biomarkers with eGFR in the patients with ARPKD (correlation coefficients for T_1: $r = -0.47$ ($P = 0.10$), T_2: $r = -0.41$ ($P = 0.17$), perfusion: $r = 0.48$ ($P = 0.09$), data not shown) was not significant for this initial study.

In Supplementary Figure S1, we depict a visual 3-dimensional comparison for these 3 MRI biomarkers of cystic burden (T_1, T_2) and perfusion for the ARPKD patient cohorts and healthy volunteers. Importantly, the multimodal MRI biomarkers, in combination, were able to stratify all 3 cohorts (2 ARPKD subgroups and the cohort of healthy volunteers) with limited overlap, demonstrating the utility of a multimodal MRI approach. Scans on consecutive days for a subset of patients with ARPKD ($n = 9$) revealed mean variation of 2.1% for T1, 2.8% for T2, and 16.3% for perfusion (Supplementary Figure S2). The superior precision of the kidney MRF-based T_1 and T_2 assessments are consistent with previous MRF studies in children and adults.[8]

DISCUSSION

This pilot cross-sectional MRI study in patients with ARPKD and healthy young adult volunteers suggests that these novel MRF assessments of kidney cystic burden (i.e., mean kidney T_1 and T_2) and ASL MRI assessment of kidney cortical perfusion have the potential to sensitively and reproducibly stage ARPKD kidney disease. Specifically, we showed that these 3 quantitative MRI biomarkers may be capable of distinguishing ARPKD subjects with differences in cystic burden and altered perfusion despite relatively similar renal function (Figure 1 and Supplementary Figure S1). Further, when used in combination, these MRI biomarkers can: (i) stratify ARPKD CKD subgroups; and (ii) differentiate early CKD from healthy volunteers despite relatively normal kidney function (Supplementary Figure S1).

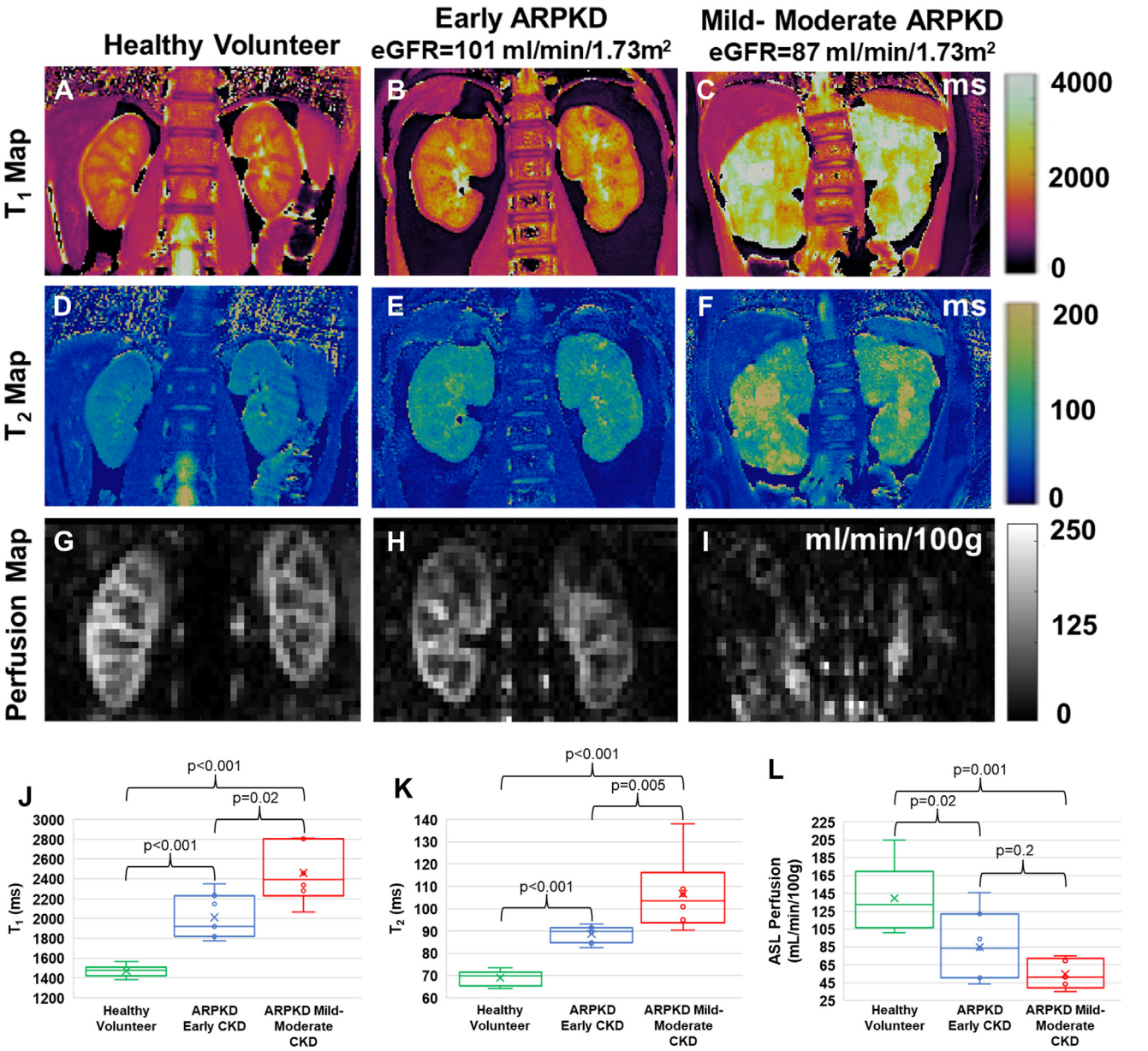

Figure 1. Multimodal imaging in patients with ARPKD and healthy volunteers. Representative kidney (a–c) T_1, (d–f) T_2, and (g–i) perfusion maps from a healthy volunteer (left column) and 2 pediatric patients with ARPKD (middle and right columns). (J–L) Box and Whisker plots for mean kidney (j) T_1, (k) T_2, and (l) perfusion from 8 healthy volunteers and 13 patients with ARPKD divided into 2 cohorts: early CKD (eGFR $\geq$ 90 ml/min per 1.73 m^2, $n = 7$) and mild to moderate CKD (eGFR 52–89 ml/min per 1.73 m^2, $n = 6$). MRI assessments of cystic burden (mean T_1 and T_2) detected significant differences between the cohorts of patients with ARPKD with early and mild to moderate CKD ($P = 0.02$ and $P = 0.005$, respectively) as well as between the patients with ARPKD with early CKD and the healthy volunteers ($P < 0.001$). The ASL-based perfusion assessments showed a significant difference between the patients with ARPKD with early CKD and healthy volunteers ($P = 0.02$) but no significant difference between the early versus mild to moderate CKD ARPKD cohorts ($P = 0.20$). All 3 MRI biomarkers showed significant differences between the volunteers and ARPKD subjects with mild to moderate CKD ($P \leq 0.001$). ARPKD, autosomal recessive polycystic kidney disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging.

The multimodal MRI methods used were obtained in ARPKD subjects aged as young as 6 years and completed within 15 minutes of scan time with no injectable MRI contrast agent or sedation. Despite the small cohort size of this pilot cross-sectional study, our findings suggest that these 3 MRI biomarkers (alone or in combination) have the potential to be used in a future ARPKD clinical trial design to: (i) identify patients with relatively intact renal function but at high risk for rapid disease progression, and/or (ii) noninvasively assess response to a new therapeutic intervention. Importantly, a larger, longitudinal study is already underway to validate these initial findings and determine the sensitivity of these MRI biomarkers to detect disease progression.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF, annotated .docx, and TIFF)

Supplementary Methods.

Supplementary References.

Figure S1. 3-dimensional visualization of multimodal MRI assessments in patients with ARPKD and healthy adult volunteers.

Figure S2. Repeatability of MRI assessments.

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